

Evaluation of the Time Saved by Prehospital Initiation of Reteplase for ST-Elevation Myocardial Infarction

Results of the Early Retavase-Thrombolysis In Myocardial Infarction (ER-TIMI) 19 Trial

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OBJECTIVES	The Early Retavase-Thrombolysis In Myocardial Infarction (ER-TIMI) 19 trial tested the feasibility of prehospital initiation of the bolus fibrinolytic reteplase (rPA) and determined the time saved by prehospital rPA in the setting of contemporary emergency cardiac care.
BACKGROUND	Newer bolus fibrinolytics have undergone only limited evaluation for prehospital administration. In addition, as door-to-drug times have decreased, the relevance of findings from prior trials of prehospital fibrinolysis has become less certain.
METHODS	Patients (n = 315) with ST-elevation myocardial infarction (STEMI) were enrolled in 20 emergency medical systems in North America. The time from emergency medical service (EMS) arrival to administration of a fibrinolytic was compared between study patients receiving prehospital rPA and sequential control patients from 6 to 12 months before the study who received a fibrinolytic in the hospital.
RESULTS	Acute myocardial infarction was confirmed in 98%. The median time from EMS arrival to initiation of rPA was 31 min (25th to 75th percentile, 24 min to 37 min). The time from EMS arrival to in-hospital fibrinolytic for 630 control patients was 63 min (25th to 75th percentile, 48 min to 89 min), resulting in a time saved of 32 min (p < 0.0001). By 30 min after first medical contact, 49% of study patients had received the first bolus of fibrinolytic compared with only 5% of controls (p < 0.0001). In-hospital mortality was 4.7%. Intracranial hemorrhage occurred in 1.0%.
CONCLUSIONS	Prehospital administration of rPA is a feasible approach to accelerating reperfusion in patients with STEMI. Valuable time savings can be achieved in the setting of contemporary transport and door-to-drug times and may translate into an improvement in clinical outcomes. (J Am Coll Cardiol 2002;40:71-7) © 2002 by the American College of Cardiology Foundation

Given the critical relationship between the time to successful reperfusion and outcomes in the treatment of patients with acute ST-segment elevation myocardial infarction (STEMI), the potential advantages of prehospital administration of fibrinolytic therapy have a sound theoretical basis (1-4). However, despite consistent evidence that prehospital fibrinolysis reduces time to treatment (5-10), and meta-analysis of results from randomized trials that suggests improved survival (11), a number of barriers have hindered the widespread development of prehospital fibrinolytic pro-

grams in North America (12,13). In part, the complexity of administering fibrinolytics that require weight-adjusted continuous infusions may have limited their use in the field. Moreover, as on-scene, transport and door-to-drug times have decreased in urban and semiurban environments, the relevance of findings from prior trials to current practice has become uncertain.

The Early Retavase-Thrombolysis In Myocardial Infarction (ER-TIMI) 19 trial was designed to test the feasibility of prehospital initiation of the bolus-fibrinolytic reteplase (rPA) and to evaluate the time saved by prehospital administration of rPA in the setting of contemporary emergency cardiac care in a diverse group of emergency medical systems in North America.

METHODS

Study centers. Patient enrollment occurred between May 1999 and July 2001 in 20 emergency medical systems across North America. The participating systems were located in 14 states in the U.S. and two provinces in Canada and

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Abbreviations and Acronyms

CI	= confidence interval
ECG	= electrocardiogram
EMS	= emergency medical service
ER-TIMI	= Early Retavase-Thrombolysis In Myocardial Infarction trial
MI	= myocardial infarction
MITI	= Myocardial Infarction Triage and Intervention trial
rPA	= reteplase
STEMI	= ST-segment elevation myocardial infarction
STRES	= ST-segment resolution

included 70 hospitals and approximately 280 ambulances. Ten systems were located in urban environments with the remainder split between semi-urban ($n = 6$) and rural ($n = 4$) environments. Ten systems were routinely performing prehospital 12-lead electrocardiography before participating in the trial. The protocol was approved by the relevant emergency medical, state regulatory and institutional review boards, and written informed consent was obtained from all patients for the collection of data regarding the primary end point, study drug administration and electrocardiogram (ECG) interpretation. In all but one center, consent for in-hospital follow-up was also obtained.

Study population. Men and women who were at least 18 years old were eligible for inclusion in the trial if they had ischemic discomfort lasting 30 min or longer within the prior 12 h and exhibited ST-segment elevation ≥ 0.1 mV in two or more contiguous limb leads or ≥ 0.2 mV in two or more contiguous precordial leads, or new left bundle branch block on a 12-lead ECG obtained in the field.

Patients were excluded if they met any of the following criteria:

1. Cardiovascular: cardiogenic shock or pulmonary edema requiring intubation; symptoms suggestive of aortic dissection;
2. Bleeding risk: single reliable measurement of systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg at any time from initial medical contact to enrollment; known prior history of stroke, transient ischemic attack, intracranial neoplasm, arteriovenous malformation or aneurysm; active bleeding or history of bleeding diathesis; major surgery, trauma or internal bleeding within prior four weeks;
3. Prior or concomitant therapy: oral anticoagulation in prior three days;
4. General: suspected cocaine or amphetamine-induced myocardial infarction (MI); known or suspected pregnancy.

Study protocol. Initial patient care conformed to Advanced Cardiac Life Support recommendations for the evaluation and treatment of patients with suspected MI. Paramedical personnel obtained a brief history, and physical examination, and evaluated the inclusion/exclusion check-

list. This information, along with a 12-lead ECG performed in the field, was transmitted via cellular or landline communications to the medical control physician who determined the patient's eligibility based upon review of the inclusion/exclusion criteria and interpretation of the transmitted 12-lead ECG. The protocol specified that eligible patients be treated immediately after enrollment with 325 mg of aspirin (unless contraindicated) and 10 U of rPA administered as an intravenous bolus over 2 min, followed by a second bolus of 10 U of rPA 30 min later. If the transport time to the hospital exceeded 30 min, the second dose of rPA was administered in the ambulance. Intravenous unfractionated heparin was administered with a bolus of 60 U/kg (maximum of 4,000 U) and an initial infusion of 12 U/kg/h (maximum 800 U/h) as soon as possible after enrollment (either in the field or hospital, depending on the transport time).

On arrival in the emergency department, patients underwent immediate evaluation by an emergency physician. If fibrinolysis was determined not to be indicated, appropriate medical therapy was undertaken without administration of the second bolus of rPA. If deemed indicated by the treating physician, patients could also be referred for immediate coronary angiography without receiving the second bolus of rPA. Use of beta-blockers, nitrates, calcium antagonists and other medications was at the discretion of the treating physician.

Clinical procedures. Heparin anticoagulated blood was obtained before administration of the fibrinolytic for performance of a rapid qualitative assay for cardiac troponin I, myoglobin and the MB fraction of creatine kinase (Cardiac STATus, Spectral Diagnostics, Frederick, Maryland). Results of the rapid assay were recorded on the case report form for investigational use only.

Standard 12-lead ECGs were performed before enrollment, upon arrival in the emergency department and 90 min after the first bolus of rPA. All available ECGs were sent to the TIMI ECG Core Laboratory (Boston, Massachusetts) for quantitative ST-segment analysis. The sum of ST deviation on the ECGs from baseline, hospital arrival and 90 min was determined using previously described methods (14), and the percent ST resolution (STRES) from baseline to emergency department arrival and baseline to 90 min was calculated for all patients with both tracings available. The STRES for each patient was categorized by two well-described classification schemes: 1) $\geq 50\%$ STRES versus $<50\%$ STRES, and 2) complete ($\geq 70\%$), partial (30% to 70%) or none ($<30\%$) (14).

End points and statistical analysis. The primary end point of the study was the amount of time saved by prehospital administration of rPA compared with in-hospital administration of a fibrinolytic in a control population of consecutive patients with STEMI transported to the hospital by ambulance and treated with a fibrinolytic in the 6 to 12 months before initiation of ER-TIMI 19. The control population was identified through pharmacy records

Table 1. Baseline Characteristics for Patients Treated With Prehospital Reteplase

Age, yrs	60 (50-71)
Men	74.5%
Weight, kg	82 (71-91)
Hypertension	47.7%
Diabetes	16.8%
Hypercholesterolemia	30.5%
Prior MI	11.8%
Prior CABG	4.6%
Prior PCI	8.9%
History of CHF	3.6%
Systolic BP, mm Hg	132 (112-150)
Heart rate, beats/min	72 (60-88)
Anterior MI or LBBB	38%*

Data for continuous variables are reported as the median and 25th to 75th percentiles. Categorical variables are reported as a proportion. *Interpreted in electrocardiogram core laboratory (n = 286).

BP = blood pressure; CABG = coronary artery bypass grafting; CHF = congestive heart failure; LBBB = left bundle branch block; MI = myocardial infarction; PCI = percutaneous coronary intervention.

of all patients receiving a fibrinolytic for STEMI in each of the hospitals participating in ER-TIMI 19. The times of emergency medical service (EMS) arrival on the scene, ambulance arrival in the hospital and initiation of the first bolus of fibrinolytic were obtained from the EMS run-logs and nursing records, respectively. The time from EMS arrival to initiation of the first bolus of a fibrinolytic was calculated for patients treated with rPA in ER-TIMI 19 and control patients treated with a fibrinolytic initiated in-hospital. The prospectively defined analysis of the primary end point was comparison of the time elapsed from EMS arrival to administration of a fibrinolytic in patients enrolled in ER-TIMI 19 versus control patients using a nonparametric mixed-effects model, including the treatment group as a fixed effect and the enrolling system as a random effect. Based upon an estimated standard deviation of 91 min for the time from EMS arrival to fibrinolytic, a sample size of 340 patients and at least as many controls was calculated to provide 99% power to detect a difference of 30 min.

Two patients were not evaluable for the primary end point due to missing times. One patient drove by car to a fire station, and the time of the first interaction was not recorded. For the second patient, the time of rPA administration was not recorded on the EMS run sheet and, thus, no source documentation was available. Clinical event rates were tabulated for all patients with available data who provided consent for in-hospital follow-up through hospital discharge or seven days. In one center, nine patients did not provide consent for follow-up of in-hospital clinical events. Five additional patients had missing data. The study was not designed for comparison of clinical event rates.

RESULTS

A total of 315 patients were enrolled in the trial. Baseline characteristics for the study population are described in Table 1. All patients received the first bolus of rPA. Because

Table 2. Reasons for Not Administering Second Bolus of Reteplase

	Number
Received 2nd bolus	301 (96%)
No second bolus	14 (4%)
Referral for immediate catheterization	4
Cardiac arrest	3
Diagnosis other than MI	1
Nondiagnostic ECG	1
Severe hypertension	1
Other/missing	4

ECG = electrocardiogram; MI = myocardial infarction.

patients were not excluded from the study based on the expected transport time, 14 patients received the first bolus of rPA after arriving in the emergency department, an average of 38 min after EMS on-scene arrival and 3.5 min after arriving in the emergency department. A total of 14 patients were treated without administration of the second bolus of rPA (Table 2). A diagnosis of acute MI was confirmed by the local investigator in 98% of patients by elevation of cardiac markers and/or evolution of diagnostic Q waves on the ECG. Of the patients without confirmed MI, one was classified as having ischemic heart disease without infarction, and five were classified as "other" by the local investigator. A rapid qualitative assay for creatine kinase-MB, cardiac troponin I and myoglobin performed on blood obtained in the field (n = 210) a median of 79 min after symptom onset was positive for at least one marker in 23% of cases. Myoglobin was elevated in 15.8% of cases, cardiac troponin I in 15.9% and creatine kinase-MB in 14.4%.

The control population was comprised of 630 patients with STEMI who had been transported by participating EMS to study centers and treated with a fibrinolytic before the date of initiating ER-TIMI 19 in each center. Limited demographic data were collected for these patients, indicating a median age of 62 years (25th to 75th percentile, 53 to 73 years) and predominance of male patients (63.3%).

Time saved by prehospital rPA. Among evaluable patients (n = 313), the median time from arrival of EMS to initiation of the first bolus of rPA was 31 min with an interquartile range of 24 to 37 min. In contrast, the time from EMS arrival to in-hospital administration of a fibrinolytic for control patients was 63 min (25th to 75th percentile, 48 to 89 min), resulting in a median time saved of 32 min (p < 0.0001). Although there was some variation in the time to administration of the first bolus across systems, the impact of introducing prehospital rPA remained highly significant (p < 0.0001) after adjusting for the effect of variability between systems. The distribution of time to treatment for patients treated with prehospital rPA and for historical controls is depicted in Figure 1. By 30 min after first medical contact, 49% of patients in ER-TIMI 19 had received the initial bolus of rPA compared with only 5% of control patients (p < 0.0001). At 1 h after EMS arrival, 97% of patients enrolled in ER-TIMI 19 had received the

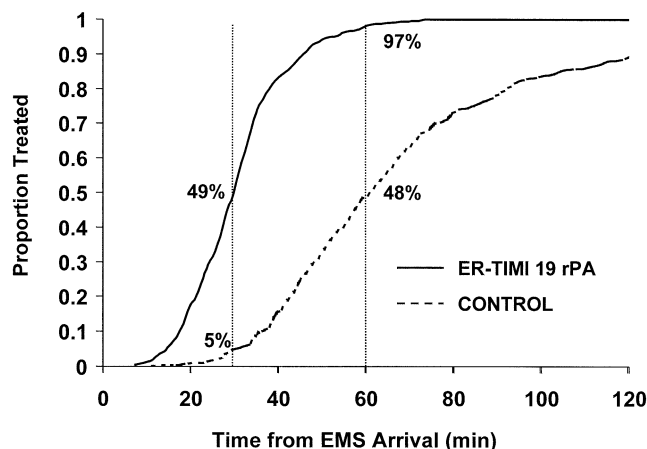


Figure 1. Cumulative distribution of time to initiation of fibrinolytic from emergency medical service (EMS) arrival for patients treated with prehospital reteplase (rPA) versus in-hospital fibrinolytic. ER TIMI 19 = Early Reteplase Thrombolysis In Myocardial Infarction 19 trial.

first bolus of rPA, whereas, reperfusion therapy had been initiated for less than half of the control population ($p < 0.0001$). The total time from EMS arrival on the scene to arrival in the emergency department, termed the “field management interval” (15), was prolonged by 14 min for patients treated with prehospital rPA compared with controls (42 vs. 28 min).

The impact of introducing a prehospital fibrinolytic program was evaluated in the context of historical performance of each system with respect to field management and door-to-drug times. The median door-to-drug time before introducing prehospital rPA was 32 min, consistent with the contemporary U.S. national average (16). When grouped by their prior performance with respect to door-to-drug times for in-hospital fibrinolysis, systems with door-to-drug times exceeding 20 min were found to achieve a significant reduction in the time to reperfusion therapy after the introduction of prehospital rPA (median time saved: 30 min for systems with historical door-to-drug times 20 to 40 min; 45 min for systems with door-to-drug times >40 min; $p < 0.0001$ for both). Similarly, EMS with field management times longer than 20 min reduced their average time to initiation of reperfusion therapy by 30 min or more with prehospital rPA (median time saved: 30 min for systems with field times 20 to 30 min; 48 min for systems with field times >30 min; $p < 0.0001$ for both).

STRES. The success of reperfusion therapy was assessed noninvasively by quantitative interpretation of the degree of STRES on the 12-lead ECG. Of the 315 baseline ECGs performed, 18 could not be interpreted for STRES due to insufficient ST deviation for quantitative determination; 5 had left bundle branch block or an accelerated idioventricular rhythm, and 6 were not available for submission to the core laboratory. Evaluable ECGs from baseline and emergency department arrival were received for 267 patients. At hospital arrival, a median of 11 min (25th to 75th percentile, 7 to 18 min) after the first bolus of rPA, 26.2% of patients

had $\geq 50\%$ resolution of the sum of ST-segment deviation at baseline. Complete ($>70\%$) STRES was observed in 13.5% of patients. A total of 237 had evaluable ECGs at baseline and 90 min. By 90 min after the initial bolus of rPA, 59.9% of patients were found to have $\geq 50\%$ STRES, with 49.4% achieving complete STRES. Expressed as a continuous variable, the median STRES observed at 90 min after rPA was 67.7% (25th to 75th, 23.9% to 86.6%). When compared with data regarding STRES from prior in-hospital fibrinolytic trials interpreted by our core laboratory (17,18), similar rates of complete ST resolution ($\sim 50\%$) were achieved 90 min after fibrinolysis. However, patients treated with prehospital rPA achieved this degree of STRES approximately 30 min earlier relative to first medical contact with the patient (Fig. 2).

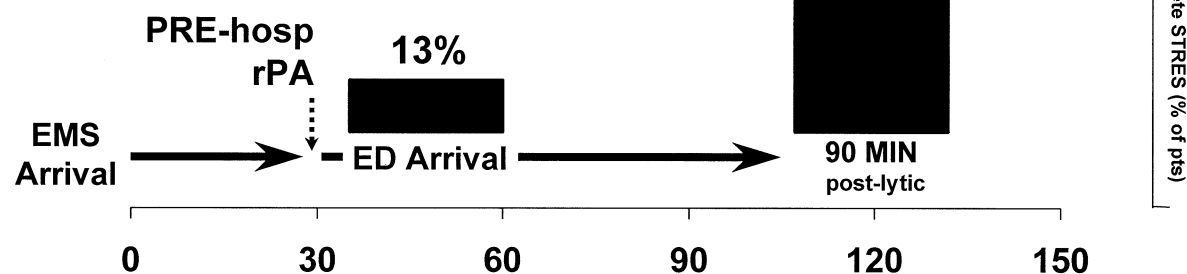
Clinical outcomes. Complete data regarding clinical outcomes were available for 301 patients. Through hospital discharge or day 7, there were 14 (4.7%, exact 95% confidence interval [CI] 2.6% to 7.7%) deaths. Five (1.7%, exact 95% CI 0.5% to 3.8%) patients had major bleeding events other than intracranial hemorrhage, and three patients (1.0%, exact 95% CI 0.2% to 2.9%) suffered intracranial bleeding. These rates are placed in the context of recent in-hospital research experience with rPA in Table 3 (19).

Sixty-five (21%) patients underwent diagnostic coronary angiography, and 56 had a percutaneous intervention performed within 6 h (median 2.4 h) after presentation. With the exception of four patients, all had received both doses of rPA. Among those patients undergoing coronary intervention, there was one major bleeding event and no intracranial hemorrhages. Twenty-four patients were treated with an adjunctive glycoprotein IIb/IIIa inhibitor (all abciximab). Procedural success as indicated by the operator was achieved in 93% of cases.

DISCUSSION

We found that with a straightforward training program paramedical personnel can act in conjunction with a medical control physician to effectively screen patients with suspected acute MI and rapidly initiate treatment with rPA for fibrinolytic-eligible patients with STEMI. Moreover, in a geographically diverse set of emergency medical systems with a large urban representation and door-to-drug times typical of the current experience in North America, administration of prehospital rPA reduced the time to reperfusion therapy by approximately 30 min, compared with historical performance, and resulted in a 10-fold increase in the proportion of patients treated within 30 min after first medical contact. In addition, our findings regarding STRES provide supportive evidence that the time to successful reperfusion was reduced among patients treated with prehospital fibrinolytic. These data extend upon prior work conducted in predominantly rural areas, single highly experienced emergency medical systems and in European centers where mobile intensive care unit teams usually include a

ER-TIMI 19



In-hospital Data

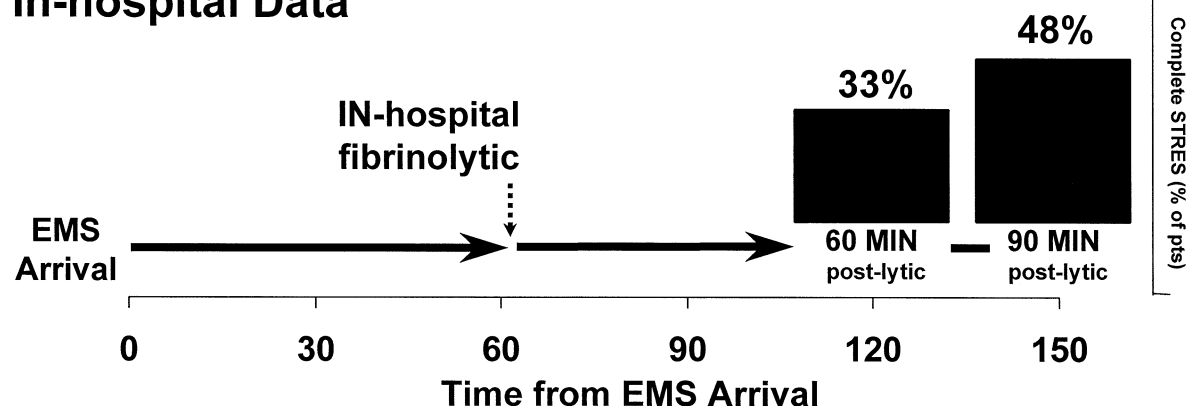


Figure 2. Proportion of patients with complete (>70%) ST-segment resolution (STRES) plotted by time from emergency medical service (EMS) arrival. Time to treatment data are from Early Reteplase-Thrombolysis In Myocardial Infarction 19 (ER-TIMI 19) trial patients treated with reteplase (rPA) and historical controls. ST-segment resolution data for patients treated with in-hospital fibrinolytic are from prior TIMI trials interpreted by the TIMI Electrocardiogram Core Laboratory, Boston, Massachusetts (17,18). ED = emergency department.

supervising physician (5–10). Our findings regarding the feasibility of and time savings with prehospital administration of rPA are likely to be applicable to a broad range of emergency medical systems in North America.

Our observations from ER-TIMI 19 are also likely to be relevant to the use of other bolus-dosed fibrinolytics (20), such as tenecteplase, which is undergoing evaluation for prehospital use in an ongoing multicenter trial. Nevertheless, by virtue of its double bolus regimen, rPA may offer greater flexibility with respect to options for further care upon arrival in the emergency department than single bolus

agents; for example, omission of the second bolus may reduce bleeding risk in patients referred for immediate coronary intervention. However, the potential clinical advantages of alternative strategies after single 10 U bolus dosing of rPA have not been evaluated in clinical trials.

Rationale for prehospital fibrinolysis. Experimental data from animal models have provided direct evidence of the critical relation between duration of arterial occlusion and the extent of irreversible myocardial injury (21–25). In the open-chest anesthetized dog, at 40 min after the onset of occlusion, 55% of the myocardium at risk remains viable, whereas by 180 min, only one-third of the jeopardized territory is salvageable (21). Data from multiple clinical studies since have supported the clinical relevance of such experimental observations, documenting a relation between time to the initiation of reperfusion therapy and survival among patients with STEMI (1,3,26–28). Particularly in the first 2 h after symptom onset, relatively small delays in treatment carry substantial implications for clinical outcomes (1,4). For example, based on a meta-analysis performed by Boersma et al. (4), treatment 30 min earlier in the first 90 min after symptom onset results in an additional 10 to 30 lives saved per thousand treated. In addition, among patients with STEMI randomized to prehospital versus

Table 3. In-Hospital Events

	Prehospital rPA Events (%)	In-Hospital rPA* Events (%)
Death	4.7	4.5
Reinfarction	3.3	3.5
Cardiogenic shock	7.3	9.4†
Major hemorrhage	1.7‡	2.3§
Intracranial hemorrhage	1.0	0.6
Nonhemorrhagic stroke	1.0	0.3

*Data from Global Utilization of Strategies to Open Occluded Arteries (GUSTO)-V, patients treated with full dose reteplase (19); †Hypotension requiring treatment; ‡Thrombolysis In Myocardial Infarction classification major hemorrhage, other than intracranial; §GUSTO-defined severe + moderate bleeding, excluding intracranial. rPA = reteplase.

in-hospital initiation of alteplase in the Myocardial Infarction Triage and Intervention (MITI) trial, those treated within the first 70 min after symptom onset had better left ventricular function and improved survival (8). Notably, the prehospital strategy in MITI increased the proportion of patients treated within that window by approximately four- to five-fold.

Together, such experimental and clinical data provide a highly consistent body of evidence supporting a rationale for treatment as soon as possible after identifying the patient with indications for fibrinolysis. Advances in technology have now made rapid evaluation of the patient with suspected myocardial ischemia possible in the field (13,29,30). Performance of prehospital 12-lead ECGs has been shown to reduce time to treatment and perhaps improve survival among patients with STEMI (31). Consistent with our findings, others have shown that paramedical personnel using prehospital electrocardiography and standardized checklists while in communication with a medical control physician can rapidly identify fibrinolytic-eligible patients with accuracy equivalent to that achieved in the emergency department (32–35). Such progress has reinforced the notion that the continuum of emergency cardiac care begins at the first medical contact with the patient, and opened the opportunity for rapid identification and earlier treatment of patients with STEMI.

Clinical implications. No single study has provided sufficiently compelling evidence to promote widespread use of prehospital fibrinolysis in North America. However, when considered in the context of previous studies, the results of ER-TIMI 19 support consideration of prehospital fibrinolytic programs for a broad base of emergency medical systems. Consistent findings across multiple trials demonstrate a time savings with prehospital fibrinolysis, ranging between 33 to 130 min, depending upon the setting (11). Meta-analysis of six randomized trials indicates a 17% reduction in the odds of death with prehospital compared with in-hospital initiation of fibrinolysis and shows no impact of whether the on-scene evaluation is conducted by a physician versus paramedical personnel (11). Such benefit appears to come without any detectable difference in the risk of major bleeding or adverse cardiovascular events with prehospital therapy (8,10). Our findings in ER-TIMI 19 demonstrate that, even with continued progress in the reduction of door-to-drug times, a prehospital fibrinolytic program saves time if either field management or door-to-drug times exceed 20 min. Thus, in light of the compelling rationale for treatment as early as possible and evidence that fibrinolysis can be targeted accurately and safely in the field, it appears that if the necessary infrastructure to support prehospital fibrinolysis is in place, there is little reason to delay treatment even if the temporal gains for any one patient may be modest.

Study limitations. Our analysis of the time saved by prehospital fibrinolysis is based on comparison of the experimental group to historical controls rather than a

randomized concurrent comparison. As the entry criteria for ER-TIMI 19 mirrored standard guidelines for determination of eligibility for fibrinolysis (36) in place before initiation of ER-TIMI 19, and were applied by the same medical control physicians, we expect that any differences in patient selection between patients enrolled in ER-TIMI 19 and the historical controls were likely to be small. Nevertheless, intrinsic to the design of trials involving comparison to historical controls, variations in patient selection may exist. Thus, although the control population was drawn from the same EMS participating in ER-TIMI 19, the possibility of heterogeneity of the patient populations and ascertainment of the treatment times remains. In addition, many of the systems participating in ER-TIMI 19 were not routinely performing prehospital electrocardiography before starting the trial. It is not possible on the basis of the data collected in ER-TIMI 19 to determine the amount of time that might have been saved in these systems by introducing performance of prehospital ECGs alone, without prehospital administration of the fibrinolytic. The results of ER-TIMI 19 do, however, demonstrate the overall time saved with introduction of a prehospital fibrinolytic program, including accurate patient identification and administration of rPA, compared with current practice in a group of emergency medical systems with diverse experience. Our findings may not be immediately relevant to centers where the primary mode of reperfusion therapy is direct percutaneous coronary intervention. However, the majority of medical centers in North America are not able to provide round-the-clock access to rapid primary angioplasty and, thus, pharmacologic therapy remains the primary mode of therapy for STEMI. Moreover, as upstream administration of a reduced dose of fibrinolytic alone or in combination with a platelet glycoprotein IIb/IIIa receptor antagonist continues to undergo study as a potential facilitator of direct angioplasty (37), it is possible that prehospital initiation of reperfusion therapy may become a desirable component of strategies for immediate percutaneous revascularization in STEMI.

Conclusions. A prehospital strategy of electrocardiography, confirmation of fibrinolytic eligibility and administration of rPA is a feasible approach to accelerating the time to reperfusion in patients with STEMI. Valuable time savings can be achieved even in the setting of contemporary transport and door-to-drug times and may translate to improved outcomes for patients treated with prehospital fibrinolysis.

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APPENDIX

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